REMARKS

Claim Amendments

Claims 13, 14, 24 and 27 have been canceled. Claims 1, 10, 20-23 and 28 have been amended.

Claims 1, 23 and 28 have been amended to recite that the method enhances the efficacy of a chemotherapeutic for inhibiting growth of a tumor. Support for the amendment can be found, for example, at page 2, lines 9-10, page 3, lines 3-7, page 9, lines 6-8 and page 10, lines 1-2 of the specification. Claims 20-22 have been amended for consistency.

In addition, claim 1 has been amended to recite that the carbohydrate comprises a polymeric backbone. Support for the amendment can be found, for example, at page 4, lines 9-10 of the specification.

Claim 10 has been amended to correct the dependency.

Claim 23 has been amended to recite a carbohydrate comprising a polymeric backbone having side chain comprising one or more sugars dependent thereof. Support for the amendment can be found, for example, at page 5, lines 5-19 of the specification.

No new matter has been added.

Rejection of Claims 4 and 23-28 Under 35 U.S.C. § 112, First Paragraph

Claims 4 and 23-28 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

Claims 4, 27 and 28 recite a carbohydrate comprising a polymeric backbone having side chains dependent therefrom, where the side chains are terminated by a galactose or arabinose unit. As acknowledged in the Office Action mailed February 15, 2006, literal support for such carbohydrates can be found at page 4, lines 9-11 of the specification. In view of this, it is not apparent why claims 4, 27 and 28 are rejected as not being adequately described. Clarification is respectfully requested.

Claim 23 has been amended to recite a carbohydrate comprising a polymeric backbone having side chains comprising one or more sugars dependent therefrom. Claim 23, as amended, is fully supported by the specification, such as at page 5, lines 5-19. This passage makes it clear that all sugars that bind galectin are contemplated, and that arabinose and galactose are merely exemplary. Claims 25 and 26 depend from claim 23, and the amendment to claim 23 is believed to address all grounds of rejection with respect to claims 25 and 26. Applicants further note that both claims 23 and 25 link the structure and the function of the recited carbohydrates, namely binding galectin or galectin-3. The specification at page 5, lines 5-19 describes the structural features of molecules having galectin-binding characteristics, such as the presence of galactose or another simple sugar and having a molecular weight greater than that of a simple sugar.

Claim 24 has been cancelled to expedite prosecution.

Applicants note the Examiner's comments regarding rhamnose residues and confirm that such residues are in the backbone of structures II and III. Applicants apologize for any factual errors made by prior counsel in the previous Amendment.

Based upon the arguments and amendments described above, claims 4, 23 and 25-28 are adequately described by the specification. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-4, 7, 13 and 18-28 Under 35 U.S.C. § 103(a)

Claims 1-4, 7, 13 and 18-28 are rejected under 35 U.S.C. § 103(a) as unpatentable over Klyosov *et al.* (US 6,645,946). Applicants include herewith copies of two Declarations Under 37 C.F.R. § 1.131 (the "Declarations"), originally submitted in Application No. 95/000,074, in which Applicants establish that the claimed invention was reduced to practice prior to the effective date of Klyosov *et al.*, March 27, 2001. The Declarations are submitted pursuant to 37 CFR § 1.47(a), as only co-inventor Yan Chang has signed. A Petition Under 37 CFR § 1.47 for the other co-inventor David Platt is filed herewith.

The experiments described in these Declarations are within the recitations of the instant claims. Although Requester in the reexamination proceedings and Dr. Platt's counsel (Exhibit **1**)

alleges that interferon-2B is not a chemotherapeutic, Applicants have already fully rebutted these assertions in the reexamination proceedings. Moreover, Applicants have provided a substantial amount of evidence that one of ordinary skill in the art would recognize interferon-2B as a chemotherapeutic.

In addition, the experiments described in the Declarations show that a carbohydrate having a polymeric backbone and which binds to a galectin enhances the efficacy of a chemotherapeutic. Although Requester in the reexamination proceedings and Dr. Platt's counsel (Exhibit 1) allege that tumors in mice treated with interferon grew at a faster pace than tumors in the mouse control group, these assertions ignore the fact that the median days of survival were calculated ***excluding*** the mice that survived, such that this statistic alone is misleading regarding the success of the experiment. In fact, the Declarations demonstrate that the average tumor size in groups receiving both GBC590B, a carbohydrate that binds galectin, and interferon consistently lagged behind that of those receiving IFN or GBC-590 alone.

The Declarations establish possession of the full scope of the claimed invention when taken in combination with the knowledge of a skilled artisan at the time. By the time of the study described in the Declarations, it was generally known in the art that modified pectin binds galectins, such as galectin-3, through its galactose residues and that other galectin-binding polymeric carbohydrates would be expected to have similar biological activities. For example, an article by Platt (a co-inventor of the instant application) and Raz ("Modulation of the Lung Colonization of B16-F1 Melanoma Cells by Citrus Pectin," Journal of the National Cancer Institute, 84: 438-442 (1992), Exhibit **2**) discusses a prior study showing that galactoside-binding lectins have been shown to mediate cell-cell adhesion and cell-extracellular matrix adhesion through carbohydrates containing terminal galactosyl residues. Based upon this prior work, the article evaluates molecules rich in galactoside residues for modulating tumor cell colonization *in vivo*. In addition, U.S. Patent No. 5,834,442 (Exhibit **3**), filed July 7, 1994 and issued November 10, 1998, states that it had been previously demonstrated that modified citrus pectin could interfere with cell-cell interactions mediated by cell surface carbohydrate-binding galectin-3 molecules. This patent then teaches that complex carbohydrates rich in galactoside residues, such as pectin, act as potent inhibitors of prostate carcinoma metastasis. Furthermore, U.S. Patent No. 5,681,923 (Exhibit **4**), filed October 6, 1995 and issued October 28, 1997, for which

co-inventor Platt is the sole inventor, discloses the sequence of galactose-specific binding polypeptides and the description of Figure 1 teaches that galactose bound to such polypeptides can be a simple sugar or a portion of a polysaccharide. Based on the inventors' knowledge of these facts and the results described in the Declarations, one of skill in the art, and in particular the co-inventors, would have expected that galectin-binding polymeric carbohydrates generally, particularly those containing terminal galactose moieties, would be useful in the claimed methods. It is particularly noteworthy that Platt, a co-inventor of the present invention, was the co-author or the sole author of references demonstrating what a skilled artisan would have known as of the effective filing date of the instant application. Thus, the experiments described in the Declarations were sufficient, in conjunction with the knowledge of a skilled artisan and the specific knowledge of the inventors, to establish possession of the claimed invention.

Because Klyosov *et al.* is available as a reference only under 35 U.S.C. § 102(a) and/or (e), the Declarations antedate the reference and are effective to overcome the rejection. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-3, 13, 14 and 18-22 Under 35 U.S.C. § 103(a)

Claims 1-3, 13, 14 and 18-22 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Green *et al.* As noted by the Examiner, Green *et al.* teach the use of glycoamines in cancer therapies.

Claim 1, from which the remaining claims depend, has been amended to recite that the carbohydrate comprises a polymeric backbone. Green *et al.* do not teach or otherwise suggest carbohydrates having a polymeric backbone. Accordingly, Green *et al.* do not teach every limitation of the claims as amended, such that the claims are not *prima facie* obvious. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-3, 12, 13 and 18-22 Under 35 U.S.C. § 103(a)

Claims 1-3, 12, 13 and 18-22 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Rubin *et al.* (US 5,639,737). According to the Examiner, Rubin *et al.* teach

that lactose or lactose conjugates of chemotherapeutic agents inhibit tumor growth and metastasis.

Claim 1, from which the remaining claims depend, has been amended to recite that the carbohydrate comprises a polymeric backbone. Rubin *et al.* do not teach or otherwise suggest carbohydrates having a polymeric backbone. Accordingly, Rubin *et al.* do not teach every limitation of the claims as amended, such that the claims are not *prima facie* obvious. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-5, 7-9, 12, 13 and 15-28 Under 35 U.S.C. § 103(a)

Claims 1-5, 7-9, 12, 13 and 15-28 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over either of Green *et al.* or Rubin *et al.* in view of Platt *et al.* The Examiner states that it would have been obvious to administer modified citrus pectin (MCP) in combination with any traditional cancer treatment.

Applicants respectfully traverse the rejection to the extent it still applies to the claims as amended. All independent claims have been amended to recite that the claimed method enhances the efficacy of a treatment for inhibiting growth of a tumor. In contrast, Platt *et al.* simply teach that MCP is effective in inhibiting metastasis. Platt *et al.* do not teach or otherwise suggest that MCP could enhance the efficacy of a treatment that inhibits the growth of a tumor. One of ordinary skill in the art would not expect an agent that inhibits metastasis would also enhance the efficacy of a treatment that inhibits the growth of a tumor. Metastasis simply involves the spread of a relatively small number of cancer cells to new areas in the body, whereas the claimed method is directed to inhibiting growth of a tumor. These two processes are mechanistically and biochemically very different processes.

The teachings of Green *et al.* and Rubin *et al.* are limited to non-polymeric carbohydrate agents, and they do not remedy this deficiency of Platt *et al.*

Furthermore, Applicants submit herewith copies of several documents indicative of the fact that the combination of a galectin-binding polysaccharide with a chemotherapeutic leads to unexpected results. First, Applicants submit a copy of the Declaration of Yan Chang under 37

C.F.R. § 1.132 submitted previously in Application No. 95/000,074, which presents data showing the effects of lactose (the anti-metastatic agent taught by Rubin et al.) and a modified pectin material (6527) on a melanoma cell line. As can readily be seen, lactose has essentially no effect on these cells, yet 6527 induces significant apoptosis. The advantage of a polymeric carbohydrate that binds to a galectin would apply when used in combination with chemotherapy, and represents an unexpected advantage of replacing lactose with such a polymeric carbohydrate viewed from the vantage of Rubin and Platt.

Also, Applicants refer back to the data presented in the Declaration of Yan Chang and David Platt under 37 C.F.R. § 1.131 submitted herewith. The data in this Declaration show a dramatic and unexpected advantage of using GBC-590 with interferon – several mice receiving combination therapy achieved tumor shrinkage, a result not seen using either therapy alone. This data is still further indication that the subject matter of the instant claims is not obvious because the heretofore untried combination produces outcomes that would have been unexpected to one of skill in the art aware of Rubin and Platt.

Applicants also submit a copy of a Declaration of Haiyong Han under 37 C.F.R. § 1.132 previously submitted in Application No. 95/000,074. This Declaration describes experiments relating to the combination of modified pectin with docetaxel, paclitaxel, and gemcitabine. The various combinations were tested using a variety of different conditions on a variety of cancer cell lines, and under many of these conditions, increased efficacy or even synergism was found, particularly for combinations with paclitaxel.

In addition, Applicants submit a copy of a Declaration of Finbarr Cotter under 37 C.F.R. § 1.132 previously submitted in Application No. 95/000,074. This Declaration describes experiments relating to the ability of etoposide, with or without modified pectin, to trigger apoptosis in cells of two different cancer cell lines. As can be seen from the attached data, the addition of GCS-100, a modified pectin, increased the efficacy of etoposide in both cell lines by increasing the number of cells that undergo apoptosis. This effect would not be expected if GCS-100 were just an antimetastatic agent. Notably, in the K562 graph, it shows that the etoposide alone requires a dose level between 100 and 500 μM to achieve a 30% level of apoptosis, while in combination with 80 μg/ml of GCS-100, similar levels of apoptosis are achieved using etoposide at a dose level between 5 and 10 μM – roughly an order of magnitude

less. The practical effect of this result is that a patient would need much less of a chemotherapeutic that may cause unpleasant side effects at higher doses, while still achieving the beneficial therapeutic results of that higher dose. This is indeed a valuable and unexpected result of the combination therapy as claimed.

Finally, Applicants submit as Exhibit **5** a copy of a recently published paper showing results of combination therapy with GCS-100 and the chemotherapy dexamethasone. The Examiner's attention is drawn in particular to Figure 4B, which depicts results of combining GCS-100 with dexamethasone on MM.1S cells. In this graph, results with GCS-100 alone (top line) and dexamethasone alone (bottom line, leftmost point at GCS-100 concentration=0) show some efficacy in reducing cell viability, but not nearly as much as a combination of both therapies (bottom line, remaining points). These results are discussed in the right-hand column of page 8354, which states towards the middle of the page: "GCS-100 significantly enhances the anti-multiple myeloma activity [] dexamethasone induced...." Figures 4C and 4D and the accompanying text demonstrate that the combined therapies activate biochemical pathways that neither therapy activates by itself.

Moreover, in the right-hand column of page 8356, this article describes how GCS-100 overcomes some mechanisms of resistance to chemotherapy: "our data show the ability of GCS-100 to overcome the cytoprotective effects of Bcl-2 in multiple myeloma cells" and "these data suggest that GCS-100 overcomes HSP-27-mediated drug resistance." The study concludes beginning on the left-hand column of page 8357: "combination therapy with GCS-100 and dexamethasone therefore may (a) allow use of subtoxic concentrations of each agent, (b) delay or prevent development of drug resistance, and (c) permit escalating additive doses of these agents to increase the apoptotic threshold." These are all advantages of combination therapy that could not have been expected for combining a mere antimetastatic agent with a chemotherapy. These are all unexpected results which further support the patentability of the claimed invention over the Examiner's proposed combinations.

In summary, Applicants have shown that the use of a polymeric carbohydrate such as modified pectin in combination with a chemotherapeutic agent confers advantages that other antimetastatic agents would not, advantages that would have been unexpected based on the art relied on by the Examiner.

For these reasons, the claimed method is not obvious over the cited references. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-5, 7-10, 12, 13 and 15-28 Under 35 U.S.C. § 103(a)

Claims 1-5, 7-10, 12, 13 and 15-28 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over either of Green *et al.* or Rubin *et al.* in view of Platt *et al.* and further in view of Ros *et al.* The Examiner states that it would have been obvious to use any method known in the art to depolymerize pectin to arrive at MCP. Ros *et al.* do not cure the deficiencies of Green *et al.*, Rubin *et al.* and Platt *et al.* discussed above because Ros *et al.* is directed simply at preparing modified pectins and has no teachings regarding the ability of carbohydrates containing a polymeric backbone and binding galectin to enhance the efficacy of a therapy for inhibiting tumor growth. Thus, for the same reasons as discussed above, the instant claims are not obvious over the cited references. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-5, 7-9, 11-13 and 15-28 Under 35 U.S.C. § 103(a)

Claims 1-5, 7-9, 11-13 and 15-28 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over either of Green *et al.* or Rubin *et al.* in view of Platt *et al.* and further in view of Renard *et al.* The Examiner states that it would have been obvious to use any method known in the art to depolymerize pectin to arrive at MCP. Renard *et al.* do not cure the deficiencies of Green *et al.*, Rubin *et al.* and Platt *et al.* discussed above because Renard *et al.* is directed simply at preparing modified pectins and has no teachings regarding the ability of carbohydrates containing a polymeric backbone and binding galectin to enhance the efficacy of a therapy for inhibiting tumor growth. Thus, for the same reasons as discussed above, the instant claims are not obvious over the cited references. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

Based upon the remarks and amendments made herein, Applicants believe that the present claims are allowable. In order to expedite prosecution, the Examiner is invited to telephone the undersigned.

Please charge our Deposit Account No. **18-1945**, from which the undersigned is authorized to draw, for any fees due or credit any overpayments under **Order No. 104831-0002-103**.

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Respectfully submitted,

By _____

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